Surgical, Pharmacological, and Technological Advances in Adult and Pediatric Urology

Highlights from the NYU Post-Graduate Medical School course
December 10-12, 1998 New York, NY

[Rev Urol 1(2):66-75, 1999]

The New York University School of Medicine Department of Urology sponsors an annual postgraduate course that addresses surgical, pharmacological, and technological advances in adult and pediatric urology. Over 300 urologists from over 40 states and 10 countries attended the 1998 course. The course is typically organized into 5 or 6 major topics and 5 to 7 state-of-the-art lectures, which rotate annually. The 5 major topics presented at the 1998 course were surgical management of stress incontinence, erectile dysfunction, renal cell carcinoma and adrenal masses, prostate cancer, and benign prostatic hyperplasia (BPH). State-of-the-art lectures were presented on prostatitis, laparoscopy, renal vascular hypertension, infertility, pediatric urology, minimally invasive urology, and bladder research. This meeting review will focus exclusively on the major topics. Affiliations of faculty members are listed on page 75.

Surgical Management of Stress Incontinence

Overview [Dr. Nitti, moderator]. The process of stress continence is multifactorial and includes urethral and bladder neck support, urethral and bladder neck intrinsic function, and the function of urethral and pelvic floor muscles. These 3 entities must be considered as both passive and dynamic processes in the maintenance of stress continence in females. Urethral and bladder neck support is often weakened in stress urinary incontinence. Formerly, it was thought that surgery to repair this defect needed to "restore the urethra to a high retropubic position." There is an increasing consensus that the goal of surgery is to re-create the supporting structures rather than simply repositioning the urethra. The intrinsic urethral sphincter is essential to the control of stress continence. It is difficult to determine how much intrinsic sphincter deficiency exists in a patient who also has support defects. In some cases, intrinsic sphincter function cannot be ascertained even with the use of sophisticated tests such as leak point pressures and urethral pressure profiles. Because of these 2 factors, there has been a change in the treatment of patients with stress urinary incontinence over the last several years. Many urologists now recommend a sling procedure as a primary treatment for patients with stress urinary incontinence, since it provides an excellent restoration of support with proven long-term results and also helps to correct any degree of intrinsic sphincter deficiency.

Evaluation of the incontinent female [Dr. McGuire]. Urethral dysfunction (stress incontinence) and bladder dysfunction (detrusor instability) are potential reasons for incontinence. Urodynamic testing is often useful to sort out the mechanisms of urinary incontinence, especially when both stress and urge incontinence coexist. The cystometrogram, however, often thought of as the gold standard for determining bladder dysfunction or detrusor instability, is normal in 50% of women who have urge incontinence. Therefore, its accuracy, specificity, and sensitivity must be questioned. On the other hand, most women who have stress incontinence will demonstrate it on urodynamic testing, and it can be measured by the use of abdominal leak point pressure.

American Urological Association Female Stress Incontinence Guidelines Panel recommendations [Dr. Dmochowski]. According to these guidelines, surgical therapy may be offered to all patients with stress urinary incontinence provided that a proper evaluation is performed and the patient is aware of options, risks, and benefits. Sling procedures and retropubic suspensions offer higher long-term cure rates for stress urinary

Meeting reviewed by Herbert Lepor, MD, New York University School of Medicine, New York, NY.

incontinence than do transvaginal suspensions and anterior repairs. At 48 months or greater, the cure rates are 83%, 84%, 67%, 61%, for these procedures, respectively.

Pubovaginal slings for stress urinary incontinence [Dr. McGuire]. Dr. McGuire recommends the classic rectus fascia pubovaginal sling for the treatment of patients with stress incontinence. In a panel discussion, the entire faculty agreed that the use of newer sling techniques and materials should not be assumed to provide the same long-term success rate as the rectus fascia pubovaginal sling.

Minimally invasive skin sling technique [Dr. Pushkar]. Using this technique, a small piece of skin about 2.4 cm is excised from the anterior wall, sutures are placed in the corners of the skin, and it is positioned via a transvaginal incision suburethrally. Cure rates are 87% and 62% at 1 to 2 years and 3 to 4 years follow-up, respectively.

Synthetic materials and bone anchoring [Dr. Dmochowski]. Most studies done on these materials have not shown significant problems. However, a review of the contemporary literature and Dr. Dmochowski's personal experience suggests that both synthetic materials and bone anchors are not without potential dangers. In particular, the development of osteomyelitis associated with bone anchors has been reported.

Treatment of mixed incontinence [Dr. Blaivas]. Is detrusor instability a contraindication to surgical treatment for stress urinary incontinence? Dr. Blaivas pointed out the inaccuracy of the cystometrogram in diagnosing detrusor instability. Multiple studies have shown no decrease in success rate for patients who have mixed incontinence compared with those who have pure stress incontinence. In some cases of mixed incontinence, the surgical management of stress incontinence is the best way to manage the overall problem.

Diagnosis and treatment of bladder obstruction following surgical treatment for stress incontinence [Dr. Nitti]. A careful history and physical are critical. Urodynamic testing is not always reliable in diagnosing obstruction. The most important predictor of obstruction is the patient's preoperative voiding and emptying history. Techniques for the management of postoperative obstruction include transvaginal urethrolysis, retropubic urethrolysis, cutting of the sling, or suspension. Urethrolysis has approximately a 70% success rate independent of the time from surgery. The 2 latter procedures would appear to offer reasonable alternatives to patients who have undergone surgery relatively recently. Recommended timing of intervention for postsurgical obstruction is: first 3 months, watchful waiting; 3 to 6 months, consider intervention, although spontaneous improvement may occur; after 6 months, spontaneous improvement is unlikely to occur.

Management of complex stress urinary incontinence with significant urethral loss [Dr. Blaivas]. The urethra can often be reconstructed from a tubularized flap of anterior vaginal wall and a pubovaginal sling with or without a Martius flap (labial fat pad). Excellent long-term results are similar to those of uncomplicated pubovaginal slings.

Periurethral bulking agents [Dr. McGuire]. Collagen remains the only FDA-approved periurethral bulking agent for the treatment of patients with stress incontinence. Periurethral bulking agents have been used primarily in patients with pure intrinsic sphincter deficiency. However, in some cases of hypermobility in the elderly with poor detrusor function, the use of collagen may be a reasonable alternative, especially when one is reluctant to perform anti-incontinence surgery for fear of a higher incidence of surgical morbidity.

Pharmacotherapy of Erectile Dysfunction

Overview [Dr. McCullough, moderator]. With the recent approval of sildenafil (Viagra®), the management of erectile dysfunction has changed dramatically. An area that had been primarily within the domain of urology is now shared with primary care physicians, cardiologists, endocrinologists, psychiatrists, or any physician who is able to write a prescription. While 95% of urologists are writing for sildenafil, only 25% of the sildenafil prescriptions are written by urologists. Fifty-six percent of prescriptions are currently written by primary care physicians.

Pharmacotherapy [Dr. McCullough]. Sildenafil has captured 95% of the male erectile dysfunction market and has demonstrated a safety profile comparable to the initial clinical trials. A recent mandatory postmarketing update of the sildenafil package insert has confirmed the safety and effectiveness of the initial clinical trials. More than 6 million prescriptions representing 50 million pills have been written. There is no evidence that sildenafil adds to the cardiovascular risk inherent in sexual activity. In addition to the reinforcement of the nitrate warning, priapism was added to the safety information. Though not reported in the clinical trial, priapism has been infrequently reported since market approval. Many of the episodes of priapism have been associated with the concomitant administration of either intracavernousal injections or intraurethral prostaglandin. The overall efficacy of sildenafil depends on the etiology of erectile dysfunction. Overall, 70% of men will experience improvement in erectile function. More severe cases of erectile dysfunction, such as in patients with severe peripheral vascular disease and following radical proctectomy, have been associated with lower response rates. Clinical trials are ongoing to

further investigate outcomes in these subgroups.

Phentolamine is a nonselective α-blocker that antagonizes both α_1 and α_2 adrenoceptors. It has been used for decades as a single or combination agent for intracavernousal injection therapy. Its mechanism of action is to block adrenergic neurotransmission in the penis. An oral form is currently under review by the FDA. Clinical trials have demonstrated efficacy of phentolamine in mild to moderate erectile dysfunction, with minimal side effects. Its onset of action is 30 minutes, and no serious adverse events were recorded in the clinical trials.

Apomorphine is currently under investigation. It has not yet been submitted to the FDA for approval. Apomorphine acts centrally and is most effective in patients with minimal organic disease. The major side effect at high doses of apomorphine is nausea.

Currently under investigation are new generations of phosphodiesterase (PDE) inhibitors that have increased selectivity for PDE5 isoenzyme, thereby minimizing visual and possibly cardiovascular side effects. These newer drugs have a more rapid onset of action.

The development of more effective transcutaneous absorption vehicles has enabled progress in the area of topical prostaglandins for the treatment of mild erectile dysfunction. The advantage of topical creams would be a more rapid onset of action and ease of use, with minimal side effects. Phase I and II clinical trials are ongoing.

Office practice in the postsildenafil era [Dr. Broderick]. The cornerstone to the workup of the patient with erectile dysfunction remains a thorough history and physical exam. The in-office diagnostic intracorporeal injection has, in fact, been replaced by a therapeutic trial of sildenafil. Diagnostic testing, such as duplex Doppler ultrasound and Rigi-Scan testing, remains an important tool in the armamentarium for the diagnostic evaluation of erectile dysfunction, particularly in the 30% of men who fail sildenafil therapy or the man who responds to sildenafil but is interested in exploring the possible physiologic cause of his erectile dysfunction.

Urologists will be called on to treat a more difficult subpopulation of patients with erectile dysfunction who fail sildenafil therapy. These men will have a higher yield of positive test results and will need more aggressive therapeutic intervention. With the increased public awareness of male erectile dysfunction, more men should seek medical attention. Though many men will seek treatment from their primary care physicians, the minority of patients who do not respond to sildenafil and, therefore, will be referred to urologists can potentially increase the volume of patients consulting urologists. If the urologist is interested in the treatment or the advanced diagnostic evaluation of erectile dysfunction, his or her practice most likely will expand.

Renal Cell Carcinoma

Overview [Samir Taneja, moderator]. The role of radical nephrectomy is constantly evolving with the advent of new surgical techniques and technology, a better understanding of the natural history of renal cell carcinoma, and the ability to diagnose the disease at early stages. Dr. Taneja raised several questions for discussion:

- When should you perform an elective partial nephrectomy for sporadic renal cell carcinoma with a normal contralateral kidney?
- Is there a role for adjuvant immunotherapies in the treatment of patients with high risk localized renal cell carcinoma?
- Are current immunomodulatory modalities for the treatment of patients with advanced disease actually impacting the natural history of the disease or are we simply selecting a population with a better prognosis?

Diagnostic imaging of renal masses [Dr. Bosniak]. Computerized tomography (CT) remains the study of choice in diagnosing and assessing renal masses. Any renal mass that enhances following the administration of intravenous contrast for CT should be considered a renal cell carcinoma until proven otherwise. The goal of the examination should be to delineate benign from malignant solid and cystic lesions. Pseudotumors, angiomyolipomas (fat containing density on CT scan), and oncocytomas (stellate scar) are lesions that can be diagnosed with CT alone. Renal cell carcinoma may be missed on CT when tumors are very small. Dr. Bosniak feels bilateral renal cell carcinoma is more common than initially thought. He has seen several cases in which a small contralateral tumor is missed at the time of nephrectomy only to be diagnosed on a later follow-up film.

Any renal mass that enhances following the administration of intravenous contrast for CT should be considered a renal cell carcinoma until proven otherwise.

The role of MRI in renal cell cancers is evolving. MRI may be most useful for evaluating the patient with renal insufficiency, evaluating the presence and extent of tumor venous extension/invasion, assessing indeterminate cystic or solid masses seen on CT, and for multiplanar 3-dimensional reconstruction of the kidney in planning a partial resection. It is critical that state-of-the-art MRI equip-

Key words

Incontinence, stress • Erectile dysfunction • Cancer, renal cell • Cancer, prostate • Benign prostatic hyperplasia (BPH)

Main Points

√ A sling procedure, the primary treatment for patients with stress incontinence, helps restore support and helps correct intrinsic sphincter deficiency.
√ The accuracy, specificity, and sensitivity of the cystometrogram in determining detrusor instability must be questioned.
√ CT alone can be used for the diagnosis of pseudotumors, angiomyolipomas, and oncocytomas.
√ Patients undergoing partial and radical nephrectomy have equivalent survival when tumors are <4 cm.
√ Patients who have a large primary tumor and who will receive immunotherapy are candidates for cytoreductive nephrectomy.
√ Age specific reference ranges of PSA for screening should not be used—a significant number of clinically relevant cancers will be missed.

ment be utilized and that the kidneys be evaluated with fat-suppression T1 and gadolinium-enhanced images.

Partial vs radical nephrectomy [Dr. deKernion]. Survival data show that survival for patients with tumors <4 cm in size is equivalent following radical and partial nephrectomy. The risk of multifocality within the kidney is estimated to be 10% to15% for T1 or T2 tumors, a risk that likely becomes greater in the setting of larger tumors. There is increased morbidity associated with partial resections, including bleeding and delayed urinary leakage. Removing a kidney in healthy individuals puts them at no additional risk of future renal compromise. Nonetheless, these patients are obviously at slight risk of injury or unforeseen damage to their solitary kidney.

Dr. deKernion's absolute requirements for a partial nephrectomy in the setting of a normally functioning contralateral kidney are that the tumor is <3 cm, favorably located in the kidney (ie, peripheral location minimizing collecting system injury and hilar dissection), and that the patient has a long life expectancy. There should be no evidence of multifocality on clinical testing. Relative indications include cystic lesions in which there is an unclear diagnosis of malignancy and a history of stone disease or transitional cell carcinoma in the contralateral kidney.

Technique of partial nephrectomy [Dr. Novick]. Partial nephrectomy is acceptable for lesions up to 4 cm. Dr. Novick's preference is an extraperitoneal/extrapleural flank incision except for very large tumors, in which case he employs a thoracoabdominal incision. In his opinion, most surgery should be performed with temporary renal ischemia, minimizing renal damage by leaving the vein patent and utilizing surface cooling of the kidney. Occluding the artery will not only reduce bleeding and improve visualization of the intrarenal structures, but also allow easier handling of the tissues due to decreased tissue turgor. The perinephric fat is excised en bloc with the tumor, and care is taken to achieve a surrounding margin of grossly normal renal parenchyma. All perihilar lymphatic attachments are divided, leaving only the hilar vessels intact. This allows the kidney to be mobilized to the skin level. Upon incision of the renal parenchyma, individual vessels are identified and ligated directly with sutures. To identify small venous branches for ligation, positive pressure ventilation by the anesthesiologist can be utilized to increase intrathoracic pressure and increase venous backflow through the kidney.

Dr. Novick reported a 30.1% overall complication rate in his own series of 259 partial nephrectomies. This included urinary fistula in 17% of patients. Only 1 patient required open repair, 14 required endoscopic management, and 30 subsided spontaneously. He stressed that a comprehensive knowledge of renal anatomy along with experience in vascular surgical techniques are imperative when attempting nephron sparing surgery.

Nephrectomy in patients with metastatic disease [Dr. deKernion]. Nephrectomy alone will not improve survival. While it has been reported that metastatic disease can spontaneously resolve after nephrectomy for renal cell carcinoma, this is not an indication for nephrectomy, because spontaneous regression occurs so rarely. Indications for nephrectomy include relief of symptoms such as hematuria, pain, and paraneoplastic syndrome. The relief of paraneoplastic syndromes such as hypercalcemia will generally only be improved by nephrectomy when the majority of disease is present in the kidney. There may exist a survival benefit from nephrectomy if there is only 1 metastatic site. Five-year survival from resection of kidney and solitary metastasis ranges from 25% to 50%, depending on the site of metastasis.

Experimental indications for nephrectomy in the presence of metastatic disease exist. These include harvesting of cells for adoptive immunotherapy and facilitating immunotherapy. In centers where cell-based immunotherapy is employed on an experimental basis, the kidney is removed to harvest lymphocytes from the primary tumor. Controversy exists about the ability of cytoreductive nephrectomy to enhance the efficacy of

cytokine-based therapies. The theoretical advantage is to remove immunosuppressive cytokines made by the primary tumor. This is probably only of advantage in patients with a large primary tumor. In patients with a small primary tumor and a large volume of metastatic disease, Dr. deKernion prefers to treat the patient with an interleukin-2 (IL-2)–based therapy with the primary in place. This is a somewhat arbitrary algorithm, but no randomized data are available to prove any survival advantage in those treated with nephrectomy prior to immunotherapy.

Management of advanced and high risk kidney cancer [Dr. Taneja]. The role of the urologist in managing patients with advanced and high risk kidney cancer has increased in recent years with the advent of IL-2–based therapy. Survival data with IL-2–based therapies show that:

1. Responses are seen in a limited number of patients.
2. Even those individuals who remain stable through therapy seem to have an improved survival compared with untreated patients.
3. One cannot conclusively determine if the effect of IL-2 on survival is true or simply a reflection of selection, but there is considerable suggestive data that the natural history is skewed in favor of patients treated with IL-2.

Dr. Taneja concurred with Dr. deKernion that cytoreductive nephrectomy is indicated in patients with a large primary tumor in place who will ultimately receive immunotherapy. Follow-up data from UCLA suggests that despite similar pretreatment performance status, age, and disease characteristics, nephrectomized patients had a higher likelihood of response when compared with patients treated with IL-2 who had the kidney in place.

IL-2 in the adjuvant setting following nephrectomy for localized renal cell carcinoma [Dr. Taneja]. No study to date has shown a benefit from adjuvant IL-2 or interferon, but these studies have suffered from a lack of rigorous inclusion criteria and poor accrual. A prospective multicenter trial randomizing high risk patients to adjuvant IL-2 or observation is being initiated by Dr. Taneja. Because of the rarity of extensive lymph node sampling at the time of nephrectomy by most surgeons, criteria for inclusion will be based strictly on tumor size.

MRI may be most useful for evaluating the patient with renal insufficiency, evaluating the presence and extent of tumor venous extension/invasion, assessing indeterminate cystic or solid masses seen on CT, and for multiplanar 3-dimensional reconstruction of the kidney in planning a partial resection.

Upon response to IL-2, extensive efforts to surgically resect residual disease may not be indicated, since recurrences usually occur in sites separate from preexisting disease. If, however, surgery achieves no evidence of disease through the resection of minimal residual disease after a significant response, this is probably of benefit.

Benign Prostatic Hyperplasia

Overview [Dr. Lepor]. The old paradigm of BPH that enlargement causes obstruction that produces symptoms is a gross oversimplification. In men with clinical BPH, α-blockers have been shown to improve symptoms and decrease obstruction. These outcomes are not likely causally related. For example, in clinical trials of α-blockers, there is little correlation between the change in symptoms and the change in peak flow rate. Men with and without bladder outlet obstruction achieve equivalent symptom improvement following administration of α-blockers. The amount of smooth muscle in the prostate predicts the improvement in flow and not symptoms. Improvement in bladder outlet obstruction is most likely mediated by relaxation of prostate smooth muscle. The symptom improvement is most likely not mediated by smooth muscle relaxation, but other intraprostatic or extraprostatic α_1 mechanisms. The recent evidence that α_{1a} selective blockers improve flow without improving symptoms provides further evidence that symptoms and obstruction are not mediated via similar mechanisms.

Clinical experiences with α_1-blockers [Dr. Brawer]. Compelling data support the efficacy and safety of α_1-blockers for the treatment of patients with BPH. The magnitude of the improvement observed with α-blockers is clinically significant, the response is durable, and the overwhelming majority of men tolerate therapeutic doses.

In Dr. Brawer's opinion, there was little advantage of tamsulosin hydrochloride (Flomax®) relative to terazosin hydrochloride (Hytrin®) and doxazosin mesylate (Cardura®), except for the lack of titration to an effective dose. The primary disadvantage of tamsulosin is that the 0.4 mg dose is less effective than the 10 mg dose of terazosin and the 8 mg dose of doxazosin while having no obvious better tolerance.

The PLESS trial [Dr. Nickel]. A post-hoc analysis of this 4-year randomized, double-blind, placebo-controlled study of finasteride (Proscar®) demonstrated that finasteride altered the risk of developing urinary retention and surgical intervention. The PLESS (Proscar Long-term Efficacy and Safety Study) trial demonstrated

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that the risk of developing urinary retention is reduced from 7% to 3% over a 4-year interval. A subset analysis demonstrated that the impact of finasteride on urinary retention is greatest in men with larger prostates. The risk of retention is also related to baseline PSA levels. Therefore, the effect of finasteride on urinary retention rates can be based on estimated prostate volume or serum PSA level. In Dr. Nickel's opinion, finasteride should be offered to men with a large prostate (>50 g) to decrease the risk of retention. In men with prostate volumes <50 g, the risk-benefit and cost-effectiveness of finasteride to reduce the risk of urinary retention is less obvious. One of the limitations of finasteride therapy is that even in men with large prostates, the effect on symptom improvement is modest at best. Therefore, men with large prostates may require both an α-blocker and a 5α-reductase inhibitor to adequately improve symptoms while reducing the risk of urinary retention.

Radiofrequency [Dr. Dixon, moderator]. The goal of radiofrequency is to deliver thermal energy directly to the prostate to ablate prostatic tissue. Transurethral needle ablation of the prostate (TUNA, Vida Med, Menlo Park, Calif) has been approved by the FDA for the treatment of patients with BPH. While a randomized study comparing transurethral prostatectomy and TUNA has reported similar symptom improvements, this does not appear to be the impression of Dr. Dixon. One of the limitations of the TUNA is that tissue impedance limits the extent of the thermal lesion. This has recently been overcome by application of a liquid electrode. Injection of saline into the prostate immediately prior to delivering the radiofrequency energy dramatically decreases the time to produce a tissue lesion and significantly increases the extent of the thermal ablation. An RFT system (US Surgical Corp, Norwalk, Conn) developed by Dr. Dixon in collaboration with US Surgical applies the virtual electrode to a radiofrequency delivery system. A significant lesion is created within 30 seconds. The RFT system is currently undergoing clinical evaluation.

Transurethral microwave thermal therapy (TUMT) [Dr. Bruskewitz]. While the high energy delivery system appears to create a greater tissue defect, it is also associated with greater morbidity than the low energy system. It is unclear whether there is a significant advantage related to symptom improvement. Several randomized trials compared TUMT to a sham procedure. The treatment related benefit of TUMT is comparable to that achieved with α-blockers. One of the primary concerns of TUMT is the durability of symptom improvement. The long-term outcomes data are inconsistent. Another limitation of the technology is the cost.

Prostate Cancer

Overview of dietary intervention [Dr. Bosland]. Epidemiologic and laboratory studies suggest that dietary intervention may play a role in the initiation and progression of prostate cancer. The incidence of occult prostate cancer is uniform throughout the world, whereas the incidence of clinical prostate cancer shows dramatic regional and racial differences. For example, the incidence of clinical cancer is far greater in the United States relative to Japan. Some of the obvious dietary differences between Japan and the United States are higher intake of fat in the United States and higher intake of soy and green teas in Japan. It is of interest that when Japanese men immigrate to the United States, the incidence of prostate cancer in the second generation immigrant is markedly increased relative to the low incidence in Japan. Further support of the importance of dietary fat in prostate cancer comes from the laboratory, where decreasing dietary fat decreased the growth rate of prostate cancer. While case control studies and laboratory findings link fat and prostate cancer risk, definitive clinical recommendations cannot be made. Prostatic intraepithelial neoplasia and prostate cancer have been identified in men as early as age 30. If dietary intervention has a role in initiating cancer, then dietary intervention must be started very early in life.

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Selenium supplementation (200 mg/d) has been reported to reduce the development of prostate cancer. The only study to show this effect of selenium was designed to determine the impact of selenium on skin cancer, and prostate cancer was a secondary end point. This observation has not been validated, and selenium has not been found to be effective in relevant animal models.

Vitamin E was also shown in a Finnish study to decrease the incidence of prostate cancer by 32%. There are epidemiologic studies failing to show an effect of vitamin E in prostate cancer. In relevant animal models, tocopherol has not been shown to be effective at reducing the growth rate of prostate cancer.

Lycopenes are present in tomatoes and are antioxidants. A single study has shown lycopenes also reduce the development of prostate cancer. This finding has not been reproduced.

Soy consumption is high in countries with low prostate cancer risk

and low in high risk countries. Soy contains several compounds with potential anticancer activities, such as the isoflavone genistein, which has antioxidant, antiangiogenesis, and antiproliferative activities. NYU Medical Center is presently conducting a randomized double-blind study to determine whether men who are at high risk for disease recurrence following radical prostatectomy benefit from 20 g/d of soy protein.

PSA screening [Dr. Brawer].

Complex PSA (cPSA) is an assay that measures the amount of PSA complexed with α_1-antichymotrypsin. The major advantage of complex PSA is that a single assay is performed. Data from studies presented by Dr. Brawer suggest that at a 95% sensitivity cutoff, cPSA is more specific than free/total PSA. If these findings are confirmed, cPSA will likely emerge as the preferred serum PSA assay.

Molecular and immunohistochemical staging [Dr. Lepor, moderator].

. . . the goal of clinical staging of [prostate cancer] should not be to predict extracapsular extension but to predict curability.

Prostate specific antigen/(PSA) is the best available screening modality for any malignancy. Nevertheless, the lack of sensitivity and specificity provides the opportunity to improve PSA-based screening. Using PSA screening alone, approximately 30% of men with PSA over 4.0 ng/dL will have prostate cancer. Thus, a significant number of men are undergoing unnecessary biopsies. Compelling evidence exists that age-specific reference ranges should not be used, since a significant number of clinically relevant cancers will not be diagnosed.

To improve the specificity of PSA screening, PSA density, PSA velocity, and free/total PSA ratios have been advocated. None of these PSA parameters have resulted in dramatic improvements in the specificity of the assay. While percent free-PSA is routinely measured, many experts often use this ratio to determine which men with normal PSA levels (between 2.5 and 4.0 ng/dL) should undergo biopsy rather than excluding men from biopsy who have PSA levels above 4 ng/dL. Determining the free/total PSA ratio increases the cost of screening, because both total PSA and free-PSA are measured individually.

The rationale for improving clinical staging of prostate cancer is that approximately 20% to 40% of men undergoing radical prostatectomy are found to have extracapsular penetration and/or positive surgical margins. It is important to recognize that a significant proportion of men with positive margins and/or extracapsular extension do not develop disease progression. Therefore, the goal of clinical staging should not be to predict extracapsular extension but to predict curability. At the present time, the Gleason score, serum PSA level, and digital rectal examination findings (clinical stage) are used to predict pathologic stage. Several investigators have reported the use of immunohistochemical staining for neovascularity, tumor suppressor genes, and oncogenes to predict pathologic stage. Recently, there was a great deal of interest in the lay press about p27, a cyclin dependent kinase inhibitor (a tumor suppressor gene) that was reported to discriminate pathologic findings. This conclusion was a gross overstatement of the results.

Seed implantation [Dr. Taneja]. The literature shows that the overwhelming majority of men with low grade tumors followed for 15 years develop disease recurrence. There has been renewed interest in seed implantation based on technologic advances that use transrectal ultrasound for seed placement and the improved radioisotopes.

Many of the contemporary studies enrolled a disproportionate percentage of men with low-grade disease. With limited follow-up to 7 years, there appears to be no marked differences between conformal radiation therapy, seed implantation, and radical prostatectomy. These data cannot be interpreted to show overall survival equivalence, since 7-year follow-up is inadequate to define cure, the definition of disease progression following radiation therapy is too conservative, and the bias for lower stage disease is not accounted for.

Performing radical prostatectomy [Dr. Lepor]. Proper positioning is essential to achieve optimal exposure. It is also important to control the dorsal vein while preserving the underlying rhabdosphincter and urethral length. Another important maneuver is to incise the reflection of the Denonvilliers' fascia overlying the anterior rectal wall at the prostatic apex before mobilizing the prostate off the rectum. Following release of the lateral pelvic fascia, the neovascular bundle is often identified. The majority of the mobilization of the pedicle to the prostate should be performed after incising Denonvilliers' fascia overlying the seminal vesicles and vasa. The ligation of the pedicle is facilitated by visualizing the lateral margin of the seminal vesicle. The plane between the seminal vesicle and bladder is developed bluntly to facilitate subsequent division of the prostatovesical junction. While an effort should be made to preserve the bladder neck, frozen sections are routinely sent to ensure that the margin is not compromised. The assistant should align

the bladder to the urethra while the eight 2-0 monocryl anastomotic sutures are tied.

Dr. Lepor reviewed his experience with the Cavermap, a device designed to assist in the intraoperative localization of the cavernous nerves. At the present time, he feels the technology is not advanced to the point that the device would be of general clinical utility. The concept is reasonable, however, and further refinements of the technology will likely lead to development of a product useful to the community-based urologic surgeon.

Prevention of local recurrences following radical retropubic prostatectomy [Dr. Taneja]. The significance of surgical margins is a grade dependent phenomenon, with better disease-free survival achieved in margin negative patients if the tumor is ≤Gleason 7. In selecting patients for nerve sparing procedures, serum PSA, Gleason grade, and palpable disease volume are the best overall predictors of extracapsular disease. New data from the group at NYU show that the position of cancer in the sextant biopsy does not predict the location of extracapsular disease. Novel data suggest the PSA density of the transition zone may be a more accurate predictor of surgical failure than PSA alone. He concluded that there is no consensus algorithm for the selection of patients for nerve-sparing prostatectomy, but suggested that the surgeon should have a low threshold for nerve excision in the setting of bulky disease, based on predictive parameters, for Gleason ≥7 disease. In the current NYU protocol for PSA recurrence, patients are observed for 6 months following failure to assess PSA velocity. Only patients with PSA <1.0 ng/dL at 6 months after first measurable PSA receive adjuvant radiation.

Management of clinical stage T1 cancer [Dr. deKernion]. Several series suggest that some men with extracapsular penetration are cured following radical prostatectomy. Often, the extracapsular penetration can be cured only in the presence of intermediate grade disease. The literature suggests no definite advantage between surgery and radiation in stage T3. □

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1999 NYU Course

The 1999 Post-Graduate Course of the Department of Urology at NYU School of Medicine will be held on December 9-11, 1999. The major topics will include lasers in urology, infertility, testicular cancer, medical management of erectile dysfunction, minimally invasive urology and stone disease, and pediatric urology. To receive a registration form for the 1999 course, fax your request to (212) 263-6303. Please include your name, address, telephone, and fax numbers.

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